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The impact of thyroid dysfunction on domain-specific cognitive performance: a cross-sectional study*

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ABSTRACT

Aims: While thyroid dysfunction has been implicated in cognitive impairment, its domain-specific effects remain unclear. This study investigates the relationship between thyroid status and performance across distinct cognitive domains in older adults.

Methods: We analyzed 166 participants (32 controls, 48 mild cognitive impairment, 86 Alzheimer's disease) aged 50-80 years without pre-existing thyroid conditions. Participants underwent comprehensive assessment including Mini-Mental State Exam (MMSE) and Clinical Dementia Rating (CDR). Thyroid status was classified by TSH levels: low (<0.55 μIU/ml), normal (0.55-4.78 μIU/ml), and high (>4.78 μIU/ml). Data normality was evaluated using the Shapiro-Wilk test, and non-parametric methods were applied due to non-normal distributions. Spearman's correlation and Kruskal-Wallis tests were used for bivariate analyses. Chi-square tests assessed associations between thyroid status and categorical variables. A multinomial logistic regression model was employed to identify predictors of thyroid status, with the low TSH group as the reference category. To address class imbalance, the SMOTE technique was applied, and multicollinearity was examined using the variance inflation factor (VIF).

Results: Among the MMSE subdomains, recall, orientation, and attention and calculation were significantly associated with thyroid status. Recall was a strong predictor for both normal and high TSH levels. Orientation scores positively predicted normal TSH and negatively predicted high TSH. Attention and calculation was significantly associated only with normal TSH. Additionally, higher CDR scores were significantly linked to high TSH status.

Conclusion: These findings suggest that rather than evaluating global cognition, domain-specific cognitive assessment may provide more meaningful insights into the cognitive effects of thyroid dysfunction.

Keywords: Thyroid dysfunction, cognitive domains, Mini-Mental State Exam, dementia, TSH, cognitive impairment

*Our study has been accepted for presentation as a poster at the European Academy of Neurology Congress 2025, which will take place on June 21–24.

INTRODUCTION

Cognitive decline is a growing global concern, particularly as aging populations expand and life expectancy increases. The World Health Organization estimates that over 55 million people worldwide live with dementia, a number expected to triple by 2050, highlighting the urgent need for preventive strategies and effective interventions to address this public health challenge.[1] Cognitive decline can result from a combination of factors, including aging, neurodegenerative diseases like Alzheimer's, vascular conditions, chronic stress, and lifestyle factors such as poor diet, physical inactivity, and lack of mental stimulation. Additionally, underlying medical conditions like thyroid dysfunction, diabetes, and depression, as well as genetic predispositions, can significantly contribute to the deterioration of cognitive function. Screening for thyroid dysfunction in patients with cognitive disorders is recommended by clinical guidelines.[2]

The hypothalamic-pituitary-thyroid axis regulates the thyroid gland, which primarily produces, stores, and releases approximately thyroxine (T4) and triiodothyronine (T3). The majority of thyroid hormones (THs) (99.8%) are reversibly bound to plasma proteins, with only the free forms of T3 and T4 being biologically active. The synthesis and release of thyroid hormones (THs) are stimulated by thyroid-stimulating hormone (TSH), which is regulated by the hypothalamus-pituitary axis. Dysfunction in the hypothalamus or pituitary can disrupt thyroid activity by altering TSH levels. THs exert negative feedback on the anterior pituitary, suppressing TSH secretion when T3/T4 levels are high and promoting it when T3/T4 levels are low.[3] Insufficiency of the levels of thyroid hormone leads to impaired neurogenesis, behavioral alterations, and cognitive deficits.[4]

Optimal central nervous system function depends on maintaining precise thyroid hormone balance in the brain, as

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even slight disturbances in cerebral hormone concentrations may lead to significant cognitive and behavioral deficits.[5]

The Mini-Mental State Exam (MMSE) is the most extensively utilized screening instrument for assessing cognitive function in older adults and is commonly employed as an outcome measure in clinical studies. The test evaluates various cognitive domains, such as orientation to time and place, immediate and delayed recall, visuospatial skills, and language abilities.[6] The Clinical Dementia Rating (CDR) is a standardized tool used to assess the severity of dementia in individuals. It evaluates cognitive and functional performance across six domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. Each domain is rated on a scale from 0 (no impairment) to 3 (severe impairment), and an overall CDR score is calculated to classify dementia stages as 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), or 3 (severe). The CDR is widely used in clinical and research settings to track disease progression and guide treatment decisions.[7]

To date, the relationship between thyroid function and cognitive decline has been extensively studied, yet a definitive association remains unclear. The aim of our study is to evaluate whether thyroid function impacts specific core cognitive domains that constitute the cognitive assessment tests, even if it does not alter the total scores. We seek to determine whether thyroid function influences individual subtests, potentially revealing subtle differences that are not reflected in the overall scoring.

METHODS

The study was initiated with the approval of the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 12.03.2025, Decision No: TABED 1-25-1083). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 166 participants were enrolled in the study, comprising 32 cognitively normal controls, 48 patients with mild cognitive impairment (MCI), and 86 patients with Alzheimer's disease (AD) (**Table 1**). While the control group was not matched to the patient groups in terms of age and gender, no statistically significant differences were observed between the groups. Participants were recruited from individuals who visited the Dementia Outpatient Clinic at Ankara Bilkent City Hospital between January and December 2024, and eligibility was determined based on inclusion and exclusion criteria. Inclusion criteria required participants to be aged between 50 and 80 years, with no history of diagnosed or treated thyroid disease. Exclusion criteria encompassed a history of insulin-dependent diabetes, uncorrected adrenal cortical insufficiency, chronic liver or kidney failure, malignancy, cerebrovascular events, head trauma, or psychiatric disorders associated with significant cognitive impairment. Additionally, individuals those with a history of treatments that could influence thyroid hormone levels, and those with recent alcohol abuse were excluded.

Table 1. Characteristics of the study population

Feature/ gender	AD (n=86)	MCI (n=48)	NC (n=32)	Total (n=166)	p-value
Gender: female (n)	36 (49.3%)	18 (37.5%)	19 (59.4%)	73	
Gender: male (n)	50 (50.7%)	30 (62.5%)	13 (40.6%)	93	
Age (mean±SD)	74.1±8.4	75.7±7.0	67.9±10.9		0.0034
fT3 (mean±SD)	3.0±0.4	3.0±0.2	3.1±0.3		0.4043
fT4 (mean±SD)	1.1±0.1	1.1±0.1	1.4±1.9		0.6258
TSH (mean±SD)	2.5±3.1	1.6±1.2	2.3±1.5		0.1114
Education (years±SD)	6.6±5.0	6.7±4.8	7.1±3.6		0.8114
Orientation (mean±SD)	4.5±2.2	6.7±1.9	9.8±0.3		0.0000
Memory (mean±SD)	2.7±0.5	2.9±0.1	3.0±0.0		0.0006
Attention & calculation (mean±SD)	1.9±1.6	3.6±1.5	4.5±0.6		0.0000
Recall (mean±SD)	0.4±0.7	0.8±0.8	2.3±0.7		0.0000
Language (mean±SD)	6.4±1.5	7.3±1.2	8.9±0.2		0.0000
Total MMSE (mean±SD)	16.1±4.2	21.4±2.9	28.6±0.9		0.0000
CDR (mean±SD)	1.9±0.8	0.5±0.0	0.0		0.0000

AD: Alzheimer disease, MCI: Mild cognitive impairment, NC: Normal control, fT3: Free T3, fT4: Free T4, MMSE: Mini-Mental State Exam, CDR: Clinical Dementia Rating, SD: Standard deviation, p-value: Indicates whether the variable is statistically significant p<0.05 is considered significant

Statistical Analysis

This study aimed to examine the relationship between patients' thyroid status and the sub-scores of the MMSE, specifically orientation, memory, attention and calculation, recall, and language. To evaluate these associations, correlation analyses and multiple logistic regression were conducted.

Prior to these analyses, the Shapiro-Wilk test was applied to assess the normality of the data. As the p-values for all variables were ≤0.05, the null hypothesis of normal distribution was rejected. Consequently, the data were considered not normally distributed at the 5% significance level. Since the data did not follow a normal distribution, Spearman's rank correlation coefficient was used for the analysis of continuous numerical variables.

In this study, a new categorical variable titled "thyroid status" was created based on the TSH values present in the dataset. Participants were classified into three groups according to their TSH levels: low thyroid (TSH <0.55 μIU/ml, shown as thyroid status=0), normal thyroid (TSH between 0.55 μIU/ml and 4.78 μIU/ml, shown as thyroid status=1), and high thyroid (TSH >4.78 μIU/ml, shown as thyroid status=2). To evaluate whether there were statistically significant differences among

these thyroid status groups, the Kruskal-Wallis test was applied, as the data did not meet the assumptions of normality required for parametric tests.

To examine the associations between gender, cognitive status, and thyroid status, separate Chi-square tests of independence were conducted. These analyses aimed to determine whether thyroid status is statistically independent from gender and cognitive status.

Following the correlation analyses, a regression analysis was performed to further examine the association between thyroid status and the independent variables, as well as to evaluate their predictive power. Given that the dependent variable (thyroid status) is categorical with more than two levels, a multinomial logistic regression model was employed. This method allowed for assessing the influence of multiple predictors on the likelihood of belonging to different thyroid status categories. Prior to modeling, multicollinearity was assessed using the variance inflation factor (VIF), which quantifies how much the variance of an estimated regression coefficient increases due to collinearity. Based on the VIF results, the Total MMSE score was excluded to avoid multicollinearity. As the thyroid status categories were imbalanced, the Synthetic Minority Over-sampling Technique (SMOTE) was applied to synthetically increase the number of samples in minority classes and prevent model bias. All categorical variables were encoded numerically, and features were standardized before building the final model.

RESULTS

According to the results, among the MMSE sub-scores, only the recall subdomain showed a statistically significant positive correlation with TSH levels (r=0.21). A strong negative correlation was observed between orientation and CDR (r=-0.76). Additionally, there were moderate negative correlations between CDR and memory (r=-0.35), CDR and attention & calculation (r=-0.61), CDR and recall (r=-0.61), and CDR and language (r=-0.58). A moderate positive correlation was also found between attention & calculation and language (r=0.41). All results were statistically significant at the 95% confidence level (**Table 2**).

The differences between thyroid status categories were assessed using the Kruskal-Wallis test. According to the results, there were no statistically significant differences among the thyroid status groups in any of the variables at the 95% confidence level. Additionally, effect sizes were found to be very small across all comparisons, indicating that thyroid status does not have a meaningful impact on these variables (**Table 3**).

According to the results, the Chi-square value for the relationship between gender and thyroid status was 5.1651, with a p-value of 0.0756. Since the p-value is greater than 0.05, it was concluded that there is no statistically significant association between gender and thyroid status. Similarly, the Chi-square value for the relationship between cognitive status and thyroid status was 4.0886, with a p-value of 0.3941. This also exceeds the 0.05 significance threshold, indicating that cognitive status and thyroid status are statistically independent of each other.

A multinomial logistic regression analysis was conducted to investigate the association between thyroid status (categorized as low TSH=0, normal TSH=1, and high TSH=2) and cognitive performance based on MMSE subdomains (**Table 4**). The reference category was defined as low TSH (0). Significant associations were found between several MMSE subdomains and thyroid status.

Orientation scores were significantly associated with normal thyroid function (OR=14.792, 95% CI: 1.729–126.572, p=0.014), indicating that higher orientation performance was associated with approximately 15-fold increased odds of being in the normal TSH group compared to the low TSH group. Additionally, Orientation was negatively associated with high TSH status (OR=0.067, 95% CI: 0.005–0.921, p=0.043), suggesting that lower orientation scores were predictive of higher TSH levels.

Attention and calculation performance was significantly associated with normal TSH status (OR=7.322, 95% CI: 2.058–26.05, p=0.002). Participants with better attention and calculation scores were more likely to have normal thyroid function compared to those with low TSH. However, this relationship was not statistically significant for high TSH (p=0.384).

Recall was a strong predictor for both normal (OR=37.639, 95% CI: 9.882–143.360, p<0.001) and high thyroid status (OR=66.890, 95% CI: 13.666–327.413, p<0.001), implying that improved recall performance was robustly associated with normal or high TSH states.

Memory was not significantly associated with normal thyroid status (p=0.332), but showed a significant positive association with high TSH levels (OR=30.860, 95% CI: 2.439–390.582, p=0.008), indicating that patients with better memory scores were more likely to be in the high TSH group.

Language did not show statistically significant associations with either thyroid category (p=0.281 and p=0.812, respectively).

CDR score was positively associated with both normal and high TSH statuses. However, statistical significance was reached only for the high TSH group (OR=54.820, 95% CI: 5.848–513.885, p<0.001), whereas the association with normal TSH did not reach significance (OR=5.028, p=0.093). This indicates that individuals with higher levels of cognitive impairment, as indicated by elevated CDR scores, were substantially more likely to be in the high TSH group relative to the low TSH group.

Cognitive Status was found to be a highly significant predictor of thyroid classification. Individuals with cognitive disease (MCI or AD) had significantly higher odds of belonging to the normal TSH group compared to those in the low TSH group (OR=162.440, 95% CI: 31.344–841.83, p<0.001).

These findings suggest that specific cognitive domains particularly recall, orientation, and attention and calculation along with clinical indicators such as CDR and cognitive status, are significantly related to thyroid hormone patterns. Notably, recall emerged as a consistent predictor for both normal and

Table 2. Spearman's rank correlation

Variable	Age	fT3	fT4	TSH	Education	Orientation	Memory	Attention and calculation	Recall	Language	CDR	Thyroid status
Age	-											
fT3	r=-0.096 p=0.2197	-										
fT4	r=0.088 p=0.2595	r=0.14 p=0.0676	-									
TSH	r=-0.057 p=0.4671	r=-0.014 p=0.8530	r=-0.064 p=0.4114	-								
Education	r=0.025 p=0.7487	r=-0.051 p=0.5105	r=0.019 p=0.8039	r=0.11 p=0.1667	-							
Orientation	r=-0.23 p=0.0027	r=0.023 p=0.7656	r=-0.08 p=0.3052	r=0.057 p=0.4621	r=0.27 p=0.0004	-						
Memory	r=-0.036 p=0.6435	r=0.03 p=0.7022	r=-0.063 p=0.4181	r=0.0038 p=0.9613	r=0.11 p=0.1777	r=0.38 p=0.0000	-					
Attention and calculation	r=0.0068 p=0.9312	r=-0.066 p=0.3991	r=-0.096 p=0.2190	r=0.016 p=0.8383	r=0.15 p=0.0528	r=0.51 p=0.0000	r=0.35 p=0.0000	-				
Recall	r=-0.21 p=0.0073	r=0.039 p=0.6147	r=-0.096 p=0.2185	r=0.21 p=0.0061	r=0.098 p=0.2095	r=0.52 p=0.0000	r=0.2 p=0.0084	r=0.33 p=0.0000	-			
Language	r=-0.1 p=0.1878	r=0.05 p=0.5253	r=0.01 p=0.8983	r=-0.029 p=0.7115	r=0.1 p=0.1896	r=0.54 p=0.0000	r=0.38 p=0.0000	r=0.41 p=0.0000	r=0.41 p=0.0000	-		
CDR	r=0.14 p=0.0664	r=-0.015 p=0.8500	r=0.034 p=0.6623	r=-0.032 p=0.6844	r=-0.062 p=0.4276	r=-0.76 p=0.0000	r=-0.35 p=0.0000	r=-0.61 p=0.0000	r=-0.61 p=0.0000	r=-0.58 p=0.0000	-	
Thyroid status	r=-0.14 p=0.0675	r=0.017 p=0.8310	r=-0.098 p=0.2097	r=0.68 p=0.0000	r=0.054 p=0.4902	r=-0.039 p=0.6186	r=0.019 p=0.8042	r=-0.043 p=0.5860	r=0.14 p=0.0783	r=-0.034 p=0.4902	r=0.045 p=0.5618	-

r: Spearman's rank correlation coefficient, p: p-value, indicates whether the variable is statistically significant p<0.05 is considered significant, CDR: Clinical Dementia Rating, fT3: Free T3, fT4: Free T4

Table 3. Kruskal Wallis test for tyroid status

	H-value	p-value	Effect size
Age	3.53	0.171	0.0094
fT3	3.14	0.2076	0.007
fT4	5.11	0.0775	0.0191
Education	2.94	0.2298	0.0058
Orientation	0.25	0.8814	0.0107
Memory	0.16	0.9242	0
Attention and calculation	0.9	0.6369	0
Recall	4.12	0.1276	0.013
Language	0.63	0.729	0
CDR	0.34	0.8416	0
Cognitive status	0.17	0.9162	0
Sex	5.13	0.0768	0.0192

fT3: Free T3, fT4: Free T4, MMSE: Mini-Mental State Exam, CDR: Clinical Dementia Rating, p-value: Indicates whether the variable is statistically significant p<0.05 is considered significant

high TSH status, while orientation, CDR score, and cognitive status provided additional insight into how cognitive function and clinical context relate to thyroid classification.

DISCUSSION

TSH levels have been widely studied in relation to cognitive function, with both hypothyroidism and hyperthyroidism being associated with cognitive impairments. THs play a critical role in brain development and function, influencing neurogenesis, synaptic plasticity, and the maintenance of cognitive processes such as memory, attention, and executive function.[8] Even subtle alterations in thyroid function, as reflected by abnormal TSH levels, can have significant effects on cognitive performance.

Numerous systematic reviews have investigated the association between thyroid dysfunction and cognitive impairment. In a review conducted by Akintola et al.,[9] out of the 15 observational studies examined, only two small cross-sectional studies found significant associations between subclinical hypothyroidism and cognitive decline, specifically affecting global cognition (as assessed by the MMSE) and memory. The other studies consistently reported no meaningful associations.

In the Danish National Patient Register (DNPR) cohort, hypothyroidism was initially linked to an increased risk of dementia, but this association diminished after adjusting for comorbidities such as cardiovascular disease and diabetes. A higher risk remained in individuals under 56, with no significant association in older adults—suggesting that younger hypothyroid patients may be more vulnerable, possibly due to the greater impact of TSH fluctuations on developing neuronal circuits.[10] A 2021 study conducted in Belgium among older adults found no significant association between thyroid dysfunction and cognitive performance, including executive function, memory, or risk of dementia.[11] Our study did not reveal any significant relationship between age and cognitive performance among patients with thyroid dysfunction.

Moreover, a Ukrainian study conducted in 2012, which included only female participants, reported a strong positive correlation between cognitive impairment and fT4 levels, along with a significant inverse correlation between MMSE

Table 4. OR results of multinominal regression model

	OR (thyroid status=1)	95% CI (thyroid status=1)	p-value (thyroid status=1)	OR (thyroid status=2)	95% CI (thyroid status=2)	p-value (thyroid status=2)
Age	0.164	0.0002208 - 1.2160	0.077	0.035	0.004-0.362	0.005
fT3	504.675	37.6815- 6759.19	0.000	42.470	2.123-849.670	0.014
fT4	10614.309	0.0000022-5.043E+13	0.415	0.000	2.731E+42-2.245E-15	0.000
Education	0.434	0.1370- 1.372	0.155	160.200	39.416-650.925	0.000
Orientation	14.792	1.729 - 126.572	0.014	0.067	0.005-0.921	0.043
Memory	0.345	0.0402-2.96	0.332	30.860	2.439-390.582	0.008
Attention and calculation	7.322	2.058-26.05	0.002	0.488	0.097-2.448	0.384
Recall	37.639	9.882-143.360	0.000	66.890	13.666-327.413	0.000
Language	3.007	0.407-22.201	0.281	0.135	0.058-9.292	0.812
CDR	5.028	0.762-33.160	0.093	54.820	5.848-513.885	0.000
Disease status	162.440	31.344-841.83	0.000	0.364	0.666-1.996	0.245
Sex	0.721	0.40 - 1.31	0.283	0.178	0.086-0.370	0.00

OR: Odds ratio, CI: Confidence interval, p-value: Indicates whether the variable is statistically significant p<0.05 is considered significant, CDR: Clinical Dementia Rating, fT3: Free T3, fT4: Free T4, Thyroid status=1: normal thyroid (TSH between 0.55 µIU/ml and 4.78 µIU/ml) thyroid status=2: high thyroid (TSH >4.78 µIU/ml)

scores and TSH levels.[12] In our study, no difference was observed between genders regarding TSH levels and total MMSE scores.

In our study, we observed that patients with low TSH levels exhibited more pronounced impairments in recall and memory subscores compared to those with normal and high TSH levels. Our findings also indicate that attention and calculation abilities tend to be more impaired in individuals with low TSH levels. This finding aligns with previous research suggesting that hyperthyroidism (low TSH levels) can lead to deficits in memory and attention, potentially due to the overstimulation of neural circuits and accelerated metabolic activity in the brain.[13] Conversely, patients with hypothyroidism (high TSH levels) showed greater impairment in orientation which may reflect the slowing of cognitive processes and reduced metabolic activity associated with thyroid hormone deficiency.[14,15] Recent research demonstrates that elevated thyroid hormone levels worsen cognitive dysfunction and accelerate β-amyloid plaque deposition in mice models through RIPK3/MLKL-mediated necroptosis and heightened neuroinflammatory responses.[16]

Our findings also revealed that CDR scores were higher in patients with low TSH levels.[17,18] Some studies propose a nonlinear association between thyroid function and cognition: both high and low TSH levels are linked to impairment, while mildly suppressed TSH (0.1–0.4 mIU/L) may correlate with optimal cognitive performance.[19]

In this study, disease status was found to be a strong predictor of thyroid classification; however, normal TSH levels were observed across all cognitive groups, including patients with AD, MCI, and cognitively healthy controls. This suggests that, although thyroid function is statistically associated with disease classification in the model, it does not appear to reliably distinguish between cognitive diagnostic categories within the studied sample. Consistent with previous findings in the literature, our results indicate that thyroid hormone levels alone may not adequately explain cognitive status, especially in clinically heterogeneous patient populations.[20,21]

The lack of a statistically significant relationship between total MMSE scores and TSH levels in our study is consistent with findings from several other studies.[22-24] This suggests that while global cognitive measures like the MMSE may not be sensitive enough to detect subtle thyroid-related cognitive changes, This highlights the assessment of cognitive function in thyroid disorders necessitates detailed neuropsychological testing beyond simple screening tools to reliably detect subtle cognitive deficits.[25,26] Despite limitations such as sample size and the lack of advanced cognitive testing, our statistically significant results may guide future studies on thyroid-related cognitive dysfunction.

CONCLUSION

As a result, our findings underscore the complex relationship between TSH levels and cognitive function. Both low and high TSH levels appear to affect specific cognitive domains, with recall and orientation being particularly vulnerable. Future studies should explore the mechanisms underlying these associations and investigate whether optimizing thyroid function can improve cognitive outcomes in affected individuals.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 12.03.2025, Decision No: TABED 1-25-1083).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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